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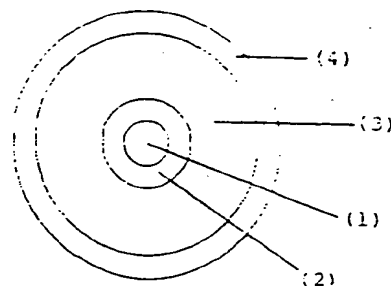
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54 Time-controlled explosion systems and processes for preparing the same.

57 Time-Controlled Explosion Systems comprising drug, swelling agent and water-insoluble coating material characterized in that drug release is caused by the explosion of membrane after a definite time period, and method for preparing it.

Fig. 1



EP 0 210 540 A1

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## TIME-CONTROLLED EXPLOSION SYSTEMS AND PROCESSES FOR PREPARING THE SAME

This invention relates to the Time-Controlled Explosion Systems and to processes for preparing the same.

For further particulars, this invention relates to the Time-Controlled Explosion Systems which have sectional structures shown in Fig. 1, 2, 3 and 4, wherein (1) is a seed of sucrose (core), (2) is a drug, (2a) is a core comprising drug, (2b) is a mixture comprising drug and swelling agent, (3) is a swelling agent, and (4) is membrane, respectively. In these systems, the drug begins to release by the explosion of the outer membrane after a definite time period (defined as "lag times") in case that it is placed into the gastro-intestinal tract. By mixing the systems which have different lag times, the oral sustained release preparations with a various release patterns such as repeat pattern - (i.e. drug release occurs repeatedly at every definite time), zero-order pattern (i.e. drug release is at uniform rate), reverse first-order pattern (i.e. drug release rate increases according to the passage of time), sigmoid pattern (i.e. drug release rate is slow at initial and last stage and is fast at middle stage) and so on can be obtained. Sustained release preparations can be used to reduce frequency of dosing, to prevent undesirable side effects and to get optimum therapeutic efficiency.

There are many approaches to prepare the sustained release preparations for the above-mentioned objects. For example, there are preparations wherein drugs are compressed with a water-insoluble materials such as waxes and plastics into a tablet form or drug-coated beads or granules are coated with the various water-insoluble coating materials. However, these preparations have disadvantages that the release rate of the drug decreases according to the passage of time, and is influenced by pH of the gastro-intestinal fluid, in case that the solubility of the drug is dependent on pH, and furthermore complete drug release from these preparations dose not occur.

An alternative approach is to prepare the sustained release preparation by mixing the granules of the non-sustained granules with the enteric-coated granules which dissolve in the intestine. As to this type of the preparations, there is possibility that the expected efficiency can not be obtained because the release of the drug is often influenced by the conditions of the gastro-intestinal tract such as pH and the emptying rate.

We have carried out various studies in order to overcome the above-mentioned problems and invented a new type of the oral sustained release dosage forms; namely, Time-Controlled Explosion Systems (hereinafter referred to as T.C.E.S.) From

the T.C.E.S., the drug is released by a quite novel mechanism which is neither diffusion control nor dissolution control. In case that T.C.E.S. are placed into the gastro-intestinal tract, gastro fluid penetrates through the outer membrane into the T.C.E.S. and swells the swelling agent incorporated into the T.C.E.S. to result in the explosion of the outer membrane. That is, the release of the drug occurred by explosion of the outer membrane. In case that the form of T.C.E.S. is tablet, drug released quickly after the explosion of the outer membrane, while in case that the form of T.C.E.S. is beads or granules, drug is released with zero order pattern after a definite lag time because of the time variance of the explosion of the outer membrane in each bead or granule.

From the extensive studies, it is found that the explosion of the outer membrane is caused by the power of swelling occurred when swelling agent absorbs the fluid. This is the reason why T.C.E.S. are not influenced by the solubility or the dissolution rate of the drug and pH of the gastro-intestinal fluid and the drug is completely released from T.C.E.S.. In addition, it is possible to get the sustained release dosage forms with various release patterns by mixing this T.C.E.S. which have different lag times. T.C.E.S. of the present invention have the following advantages; (i) the release rate or pattern is hardly influenced by the solubility or the dissolution rate of the drug, (ii) the release rate or pattern is independent of pH of the dissolution medium, and (iii) the drug is completely released. In addition, the sustained release dosage form with the various release patterns such as repeat, zero order, reverse first-order pattern, sigmoid pattern and so on can be obtained by mixing the T.C.E.S. which have different lag times. In case that the form of T.C.E.S. is tablet, repeat pattern can be obtained by combining with non-sustained preparation. The lag times can be controlled by the sort of the swelling agent and membrane, and the size of T.C.E.S.. The suitable form of T.C.E.S. may be, for example, bead, granule and tablet. Both basic drugs and acidic drugs are applied to T.C.E.S. of the present invention. Basic drugs are, for example, Metoclopramide, Sulpiride, Metoprolol tartrate, Tiapride, Zotepine, Cimetidine, etc. Acidic drugs are, for example, Diclofenac, penicillin and cephalosporine antibiotics, etc. Among these drugs, water-insoluble drug like FK235 substance may be converted, for example, into water-soluble solid dispersion composition. This solid dispersion composition is prepared by dispersing said drug in

water-soluble polymer [e.g. hydroxypropylmethylcellulose, polyethylene glycol derivatives (e.g. polyethylene glycol 6000, polyethylene glycol 1500, etc.), etc.].

One type of T.C.E.S. of the present invention in which the form is beads or granules can be prepared as follows. Firstly, the drug-coated or drug-comprised beads and granules are prepared by conventional procedures. For example, nonpareil (granule of sucrose; Trademark; prepared by Freund Co., Ltd.) seeds are placed and rolled in centrifugal granulator or blown up by air in fluid bed granulator. Drug is coated on the seeds with spraying binder (e.g. hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, sodium alginate, etc.) dissolved in a suitable solvent (e.g. water, ethanol, etc.). An alternative method which makes beads or granules comprising drug, diluents (e.g. sucrose, lactose, mannitol and microcrystalline cellulose and the like) and additives used ordinarily in this field by conventional procedures is also available. Next, the swelling agent is coated on the drug-coated or drug-comprised beads and granules by the same procedure described above. The swelling agents used are, for example, disintegrating agent [e.g. low substituted hydroxypropylcellulose, carboxymethylcellulose calcium, Ac-Di-Sol (carboxymethylcellulose sodium; Trademark; prepared by FMC Inc.), Explotab (sodium starch glycolate; Trademark; prepared by Edward Mendell Co., Ltd.), starch, agar, etc.], synthesized polymer, (e.g. polyvinylacetate, polyacrylic acid, acrylate copolymer, polyethylene glycol, etc.), inorganic salt (e.g. magnesium chloride, calcium sulfate, etc.), organic salt (e.g. sodium carbonate, calcium bicarbonate, etc.), sugar (e.g. d-mannitol, sucrose, glucose, etc.), tartaric acid, albumin, urea, and the like. Low substituted hydroxypropylcellulose is defined as cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent. The effervescent agents (e.g. mixture of sodium bicarbonate and tartaric acid, etc.) may be used instead of the swelling agents. The number of layer of the drug and the swelling agent are not limited to one respectively in T.C.E.S.. That is, several drug layers and several swelling agent layers can be coated alternatively according to the same procedure as described above, if necessary, to get various release patterns. The ratio of the drug and the swelling agent in the beads or granules is preferably 0.1 to 50 and 30 to 80 weight percent respectively, but is not restricted to the above ratio, and can be changed in accordance with the dose or the lag times to be required respectively. Another type of T.C.E.S. of the present invention in which the form is beads or granules can be prepared firstly as follows. Nonpareil seeds are coated with a mixture of drug and

swelling agent by the same procedure as described above. An alternative method which makes beads or granules comprising drug, swelling agent, diluents (e.g. sucrose, lactose, mannitol and microcrystalline cellulose and the like) and additives used ordinarily in this field by conventional procedures is also available. The ratio of the drug and the swelling agent in the beads or granules is the same as one exemplified above. Another type of T.C.E.S. of the present invention in which the form is tablet can be prepared firstly according to conventional procedure, for example, by compressing the mixture of drug, swelling agent, diluents and lubricants (e.g. magnesium stearate, etc.). The ratio of the drug and the swelling agent in the tablet is preferably 0.1 to 30 and 10 to 60 weight percent respectively, but is not restricted to the above ratio. Finally, swelling agent-coated or comprised beads, granules and tablet prepared by the methods described above are coated with the water-insoluble coating material with additives (e.g. talc, polyethylene glycol, silicone, diethylsebakate, and titanium dioxide and the like) to form outer membrane by conventional procedures. For example, the above-mentioned preparations are placed and blown up by air in fluid bed granulator, and then water-insoluble coating material dissolved in a suitable solvent (e.g. ethanol, dichloromethane, etc.) and additives are coated on the above-mentioned preparations. The water-insoluble coating material used is, for example, ethylcellulose, hydroxypropylcellulose, shellac, polymethylstyrene, polyvinylacetate, polydiethylaminomethylstyrene, dimethylaminoethylmetacrylate-methylmetacrylate acid-co-polymer [e.g. Eudragit E-30D, Eudragit RL, Eudragit RS (Trademarks; prepared by Röhm Pharma Co., Ltd.)] and wax and the like. Among these water-insoluble coating materials, ethylcellulose is preferable because ethylcellulose membrane is easy to explode when the swelling agent is swelled. The ratio of the water-insoluble coating material for the above-mentioned preparations is preferably 1 to 50 weight percent, but is not restricted to the above ratio, and can be changed in accordance with the lag times to be required. The size of T.C.E.S. of the present invention is preferably 0.5 mm to 20 mm in diameter. To illustrate the effect of T.C.E.S. of the present invention, dissolution test data and absorption test data are shown in the following.

#### Dissolution Test 1

##### Test preparations (Drug : Metoclopramide)

Sample A : Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 7.0 weight %

Sample B : Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 14.2 weight %

Sample C : Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 29.4 weight %

Sample D : Preparation disclosed in Reference 1 in which the concentration of ethylcellulose is 5.0 weight %

Sample E : Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of three to one

Sample F : Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of one to one

Sample G : Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of one to three

Sample H : Preparation disclosed in Example 9

Sample I : Preparation disclosed in Example 10

Test method (I) The pharmacopoeia of Japan 10th edition

Dissolution method II (Paddle method)

Dissolution medium : First fluid (pH 1.2)

900ml, 37°C, 100r.p.m.

(II) The pharmacopoeia of Japan 10th edition

Dissolution method II (Paddle method)

Dissolution medium : Second fluid (pH 6.8)

900ml, 37°C, 100r.p.m.

Test result

Dissolution test data are shown in Tables 1, 3, 4 and 5.

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Table 1

Test Prepara- tion	Test method	Dissolution rate (%)									
		0.5hr	1 hr	1.5hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Sample A	I	5	63	91	95	98	99	100	100	100	100
	II	4	54	90	95	98	99	100	100	100	100
Sample B	I	0	0	0	4	29	83	99	100	100	100
	II	0	0	0	3	26	81	99	100	100	100
Sample C	I	0	0	0	0	0	8	55	90	99	100
	II	0	0	0	0	0	6	54	85	96	100

Table 2

Test Prepara- tion	Test method	Dissolution rate (%)									
		0.5hr	1 hr	1.5hr	2 hr	3 hr	4 hr	5 hr	6 hr	8 hr	10 hr
Sample D	I	21	38	49	56	64	68	72	74	78	83
	II	0	3	5	8	10	12	13	14	18	20

Table 3

Test Preparation	Test method	Dissolution rate (%)									
		0.5hr	1 hr	1.5hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Sample E	II	2	38	68	74	75	76	84	95	99	100
Sample F	II	2	30	46	48	49	51	69	87	96	99
Sample G	II	1	12	22	24	25	29	47	77	91	98

Table 4

Test Preparation	Test method	Dissolution rate (%)				
		1 hr	2 hr	4 hr	6 hr	8 hr
Sample H	I	2	20	98	100	100
	II	0	14	91	99	100

Table 5

Test Preparation	Test method	Dissolution rate (%)			
		1 hr	1.25 hr	1.5 hr	2 hr
Sample I	II	0	95	98	100

Test method

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Dissolution Test 2

Test methods are the same as ones described in Dissolution Test 1.

Test preparations (Drug : Metoprolol tartrate)

Sample J : Preparation disclosed in Example 8

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Test result

Sample K : Preparation disclosed in Reference 2 - (control)

Dissolution test data are shown in Table 6.

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Table 6

Test Prepa- ration	Test method	Dissolution rate (%)							
		0.25 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr
Sample J	I	0	1	2	39	67	92	95	100
	II	0	0	2	20	89	94	99	100
Sample K	I	100	-	-	-	-	-	-	-
	II	100	-	-	-	-	-	-	-

## Absorption Test

## Test method

Test preparations (Sample J and Sample K) were administered orally to three Beagle dogs weighing about 10 kg that were fasted overnight respectively.

Dose of each test preparation was 120 mg as Metoprolol tartrate. 0.5, 1, 2, 4, 6, 8 and 10 hours after oral administration, blood was collected into a heparinized tube. After centrifuging, plasma concentrations of Metoprolol were measured by high pressure liquid chromatography.

## Test result

Test result is shown in Table 7. Plasma concentration was shown by mean-value of three dogs.

Table 7

Test Prepa- ration	plasma concentration (ng/ml)						
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr
Sample J	N.D.	N.D.	61	479	294	172	109
Sample K (control)	519	752	736	412	150	112	79

( N.D.: plasma concentration was not detected )

Release patterns of the T.C.E.S. of the present invention in which the drug and the swelling agent are separated are shown in Table 1. These data show that the drug begins to release after a definite time and the drug is completely released with the zero-order pattern after the sample is subjected to the dissolution test. As shown in Table 1, the lag

times increase with the membrane thickness. In addition, the release rate and pattern is independent of pH, whereas, as shown in Table 2, the drug containing beads coated with the membrane in the absence of the swelling agent (Sample D) give the release rate which is dependent on pH of the dissolution medium and the drug is not completely

released from this beads even after 10 hours, though the membrane is thinner than the above T.C.E.S. of the present invention (i.e. Samples A to C).

The representative release patterns of the drug from the mixture of Sample A and Sample C are shown in Table 3.

As apparent from Table 3, T.C.E.S. of the present invention provide for the new type of the oral sustained release preparations in which the release rate and pattern are freely controlled. Release pattern of the another type of T.C.E.S. of the present invention in which drug and swelling agent are mixed is shown in Table 4. Release pattern is almost the same as ones of T.C.E.S. as stated above in which the drug and the swelling agent are separated. Release pattern of the T.C.E.S. in which the preparation form is tablet is shown in Table 5. As shown in Table 5, drug is released quickly from this type of T.C.E.S. after a definite lag time. Absorption test data are shown in Table 7. These data show that plasma concentration of Metoprolol is not detected until 1 hour, slightly detected at 2 hour

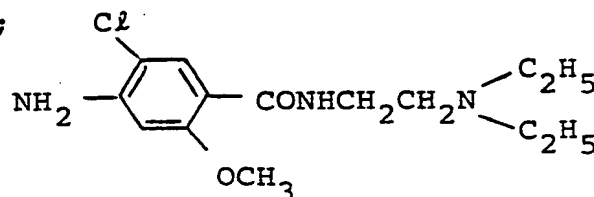
and is attained to maximum at 4 hour after oral administration of T.C.E.S. of the present invention (Sample J), whereas high plasma concentration is detected at 0.5 hour after oral administration of Sample K (control). This absorption test data reflects the dissolution test data shown in Table 6, namely, Metoprolol is not released until 1 hour, slightly released at 2 hour and mostly released at 4 hour from T.C.E.S. of the present invention (Sample J). These data suggest that sustained plasma concentration can be obtained by mixing T.C.E.S. which have different lag time, for example shown in Table 1.

As mentioned above, the T.C.E.S. of the present invention have many excellent advantages and have solved many problems of the prior arts.

The present invention is illustrated according to the examples as shown below, but is not limited thereto. The chemical names and formulae of the drugs in the examples are shown below.

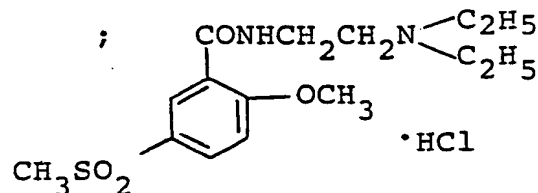
(i) Chemical name: 2-methoxy-4-amino-1-chloro-N( $\beta$ -diethylaminoethyl)benzamide (Metoclopramide)

Formula



(ii) Chemical name: N-[2-(diethylamino)ethyl]-5-(methylsulfonyl)-o-anisamide hydrochloride (Tiapride)

Formula



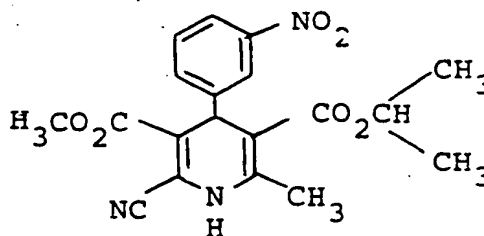
(iii) Chemical name: 5-isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate (FK235 substance)

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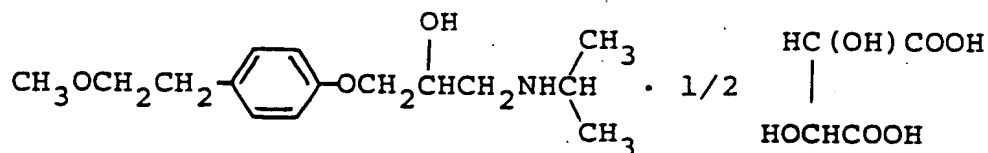
Formula ;



(iv) Chemical name: dl-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol hemi-L-tartrate (Metoprolol tartrate)

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Formula ;



#### Example 1

Nonpareil seeds (2 kg) were placed and rolled in a centrifugal granulator. Metoclopramide (670 g) was coated on said Nonpareil seeds with spraying hydroxypropylmethylcellulose (36 g) dissolved in water (720 g).

#### Example 2

The drug-coated beads (1.05 kg) prepared in Example 1 were placed and rolled in a centrifugal granulator. Low substituted hydroxypropylcellulose (1.65 kg) was coated on said beads with spraying hydroxypropylmethylcellulose (0.209 kg) dissolved in ethanol-water mixture (85:15 V/V %) (4.18 l).

#### Example 3

The swelling agent-coated beads (100 g) prepared in Example 2 were placed and blown up with air in a fluid bed granulator. Ethylcellulose dissolved in ethanol and talc was sprayed to coat on said beads to give the desired preparations. Three

preparations wherein the concentration of ethylcellulose is 7.0, 14.2 and 29.4 weight % for the beads prepared in Example 2 were prepared.

#### Example 4

Time-Controlled Explosion System, wherein core is Nonpareil seed (420 g), drug is Metoclopramide (140 g), swelling agent is Explotab (840 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3. The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 17.7 weight %.

#### Example 5

Time-Controlled Explosion System, wherein core is Nonpareil seed (420 g), drug is Metoclopramide (140 g), swelling agent is Ac-Di-Sol (840 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3. The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 21.8 weight %.

## Example 6

Time-Controlled Explosion System, wherein core is Nonpareil seed (778 g), drug is Tiapride - (158 g), swelling agent is low substituted hydroxypropylcellulose (870 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3. The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 21.2 weight %.

## Example 7

FK235 substance (2 g) was dissolved in a mixture of polyethylene glycol 1500 and polyethylene glycol 6000 (1:1 W/W) (100 g) with heating. After cooling, granules which contain FK235 substance were prepared according to the conventional method. Thereafter, Time-Controlled Explosion System, wherein swelling agent is low substituted hydroxypropylcellulose (500 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 2 and 3. The concentration of ethylcellulose for the granules prepared according to a similar procedure to that of Example 2 is 10.5 weight %.

## Example 8

Time-Controlled Explosion System, wherein core is Nonpareil seed (392 g), drug is Metoprolol tartrate (168 g), swelling agent is low substituted hydroxypropylcellulose (840 g) and water-insoluble

coating material contains ethylcellulose and talc was prepared according to similar procedures those of Examples 1, 2 and 3. The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 12.6 weight %.

## Example 9

Nonpareil seeds (500 g) were placed and rolled in a centrifugal granulator. Metoclopramide (170 g) and low substituted hydroxypropylcellulose (100 g) were mixed and the mixture was coated on the nonpareil seeds with spraying hydroxypropyl methylcellulose (150 g) dissolved in ethanol-water mixture (85:15 V/V %) (31). Ethylcellulose dissolved in ethanol and talc was sprayed to coat the seeds as obtained to give Time-Controlled Explosion System. The concentration of ethylcellulose for the beads as obtained is 13.2 weight %.

## Example 10

Metoclopramide (7.7 g), lactose (42 g), microcrystalline cellulose (30 g), Ac-Di-Sol (20 g) and magnesium stearate (0.3 g) were mixed and the mixture was compressed into tablets. Ethylcellulose dissolved in ethanol was sprayed to coat on the tablets to give Time-Controlled Explosion System.

One tablet has the following formula :

Metoclopramide	7.7 mg
lactose	42 mg
microcrystalline cellulose	30 mg
Ac-Di-Sol	20 mg
magnesium stearate	0.3 mg
ethylcellulose	5.2 mg
<hr/>	
	105.2 mg

## Reference 1

For the purpose of comparing with the preparation prepared in Example 3, Metoclopramide beads (105 g) coated with ethylcellulose without swelling agent were prepared according to similar procedures to those of Examples 1 and 3 without the process described in Example 2. The concentration of ethylcellulose for the Metoclopramide beads is 5.0 weight %.

## Reference 2

For the purpose of comparing with the preparation prepared in Example 8, Metoprolol tartrate beads (560 g) without swelling agent and water-insoluble coating material were prepared according to a similar procedure to that of Example 1.

Brief description of the drawings are as follows. Fig. 1 shows a sectional structure of T.C.E.S. disclosed in Examples 3 to 6 and 8 in which (1) is a seed of sucrose (core), (2) is a drug, (3) is a swelling agent and (4) is membrane respectively. Fig. 2 shows a sectional structure of T.C.E.S. disclosed in Example 7 in which (2a) is a core comprising drug (3) is a swelling agent and (4) is membrane respectively. Fig. 3 shows a sectional structure of T.C.E.S. disclosed in Example 9 in which (1) is a seed of sucrose (core), (2b) is a mixture comprising drug and swelling agent and (4) is membrane respectively. Fig. 4 shows a sectional structure of T.C.E.S. disclosed in Example 10 in which (2b) is a mixture comprising drug and swelling agent and (4) is membrane respectively.

## Claims

1. Time-Controlled Explosion Systems comprising drug, swelling agent and water-insoluble coating material characterized in that drug release is caused by the explosion of membrane after a definite time period.

2. Time-Controlled Explosion Systems according to claim 1, wherein drug and swelling agent are separated.

3. Time-Controlled Explosion Systems according to claim 1, wherein drug and swelling agent are mixed.

4. Time-Controlled Explosion Systems according to claim 1, wherein water-insoluble coating material comprises ethylcellulose.

5. Time-Controlled Explosion Systems according to claim 1, wherein swelling agent is disintegrating agent.

6. Time-Controlled Explosion Systems according to claim 5, wherein disintegrating agent is low substituted hydroxypropylcellulose, sodium starch glycolate or carboxymethylcellulose sodium.

7. Time-Controlled Explosion Systems according to claim 1, wherein the form of the preparation is bead, granule or tablet.

8. Time-Controlled Explosion Systems according to claim 1, characterized in mixing the systems which have different lag times to get the sustained release preparations with various release patterns.

9. A method for preparing Time-Controlled Explosion Systems in which drug release is caused by the explosion of membrane after a definite time period characterized in that after preparing beads or granules comprising drug, swelling agent is firstly coated thereon and then water-insoluble coating material is coated thereon.

10. A method for preparing Time-Controlled Explosion Systems in which drug release is caused by the explosion of membrane after a definite time period characterized in that after preparing beads, granules or tablets comprising drug and swelling agent, water-insoluble coating material is coated thereon.

Fig.1

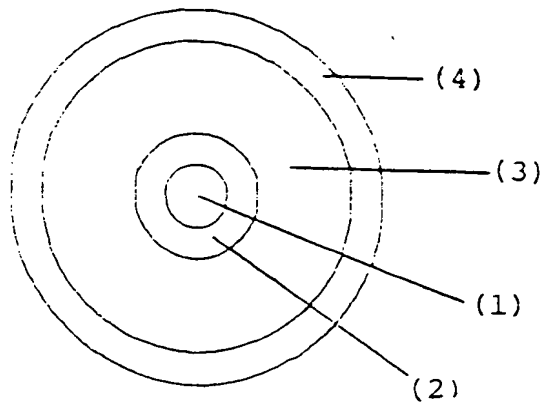


Fig.2

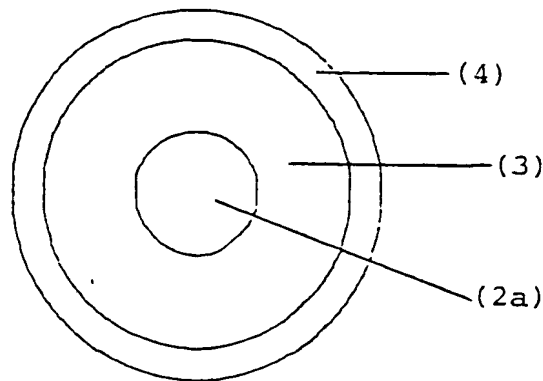


Fig.3

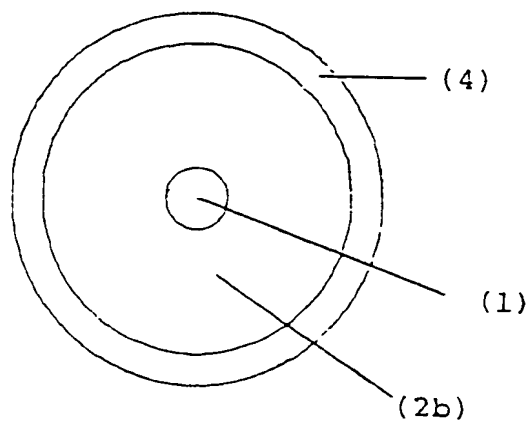
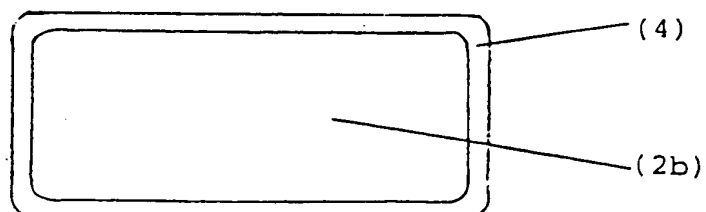


Fig.4





European Patent  
Office

# EUROPEAN SEARCH REPORT

Application number

EP 86 10 9733

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	DE-A-1 617 724 (PARKE, DAVIS & CO.) * Whole document *	1-10	A 61 K 9/52 A 61 K 9/36
X	FR-A- 848 389 (LIPOWSKI) * Page 1, lines 1-11; page 2, lines 5-80; page 3, lines 39-70; claims 18-21 *	1-10	
A	EP-A-0 077 956 (TANABE SEIYAKU) * Page 1, lines 1-9; page 5, line 17 - page 7, line 1; claims 9-11, 23-25 *		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 30-10-1986	Examiner BENZ K.F.
CATEGORY OF CITED DOCUMENTS			
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